REMARKS

The Amendment

In the interest of expediting the prosecution of the present application, Applicants are amending Claims 32, 38, and 44, and canceling Claims 33-37, and 41. Applicants reserve the right to reintroduce the originally filed claims in one or more continuation applications.

Paragraph [38] was amended to capitalize the trademark term "GENBANK®".

Paragraph [45] and the paragraph beginning on page 109, line 1 were amended to enter SEQ ID NOs.

Paragraphs [38], [54], and [57] were amended to delete the reference to the hyperlinks.

Paragraph [188] was amended to capitalize the trademark term "TEFLON®".

Paragraphs [237], [243], and [244] were amended to capitalize the trademark term "TRIZOL®".

Paragraphs [237], [254], and [272] were amended to recite the chemical formula "H_2O".

Paragraphs [238], [242], and [243] were amended to capitalize the trademark term "SORVALL®".

Paragraphs [238], [242]-[245], [259]-[261], [265], [269], and [270] were amended to recite the correct "°" symbol.

Paragraphs [254] and [264] were amended to recite the chemical formula "NH_4OAc" in the correct font.

Paragraphs [254]-[259], [261], [264], [265], [268], [271], and [272] were amended to recite "µg" or "µl" instead of "ug" or "ul", respectively.

Paragraph [272] was amended to capitalize the trademark term "QIAGEN®".

Claim 32 was amended to recite the term "a human patient". Support for the amendment is found, for example, in paragraph [223].

Claim 32 was amended to recite the phrase "obtaining a sample comprising colorectal tissue from a human patient". Support for the amendment is found, for

example, in paragraph [26].

Claim 32 was amended to recite the phrase "detecting the level of a polynucleotide encoding a CBF9 polypeptide in the sample, wherein the polynucleotide is an RNA equivalent of a nucleic acid sequence at least 90% identical to the nucleic acid sequence disclosed in SEQ ID NO: 1". Support for the amendment is found, for example, in paragraphs [14], [95], and [139].

Claim 32 was amended to recite the phrase "wherein an increase in the level of the polynucleotide relative to normal colorectal tissue is indicative of cancer". Support for the amendment is found, for example, in paragraph [38].

Claim 38 was amended to replace the term "expression" with the term "level". Support for the amendment is found, for example, in the first line of paragraph [26].

Claim 44 was amend to recite "said polynucleotide is an RNA equivalent of the nucleic acid sequence disclosed in SEQ ID NO:1". Support for the amendment is found, for example, in paragraphs [14], [36], and [139].

Support for new Claim 45 is found, for example, in paragraph [35].

Support for new Claims 46, 53 and 62 is found, for example, in paragraphs [59] and [167].

Support for new Claims 47, 54, 64, 67, and 68 is found, for example, in paragraph [167].

Support for new Claims 48 and 55 is found, for example, in paragraphs [59] and [72].

Support for new Claims 49 and 56 is found, for example, in paragraphs [14] and [36].

Support for new Claims 50 is found, for example, in paragraphs [14], [38], [95], and [223].

Support for new Claims 51 and 58 is found, for example, in paragraph [144].

Support for new Claim 52 is found, for example, in paragraph [38].

Support for new Claim 57 is found, for example, in paragraph [14].

Support for new Claim 58 is found, for example, in paragraph [15].

Support for new Claims 59 and 66 is found, for example, in paragraph [15].

Support for new Claim 60 is found, for example, in paragraphs [14], [38], [95], [136], [137], and [223].

Support for new Claim 61 is found, for example, in paragraph [139].

Support for new Claim 63 is found, for example, in paragraph [167].

Support for new Claim 65 is found, for example, in paragraph [140].

No new matter is added by any of the above amendment and the Examiner is respectfully requested to enter the amendments and reconsider the application.

Response

Claims 32-44 stand rejected. With the entry of the amendments presented herein, Claims 32, 38-40, and 42-59 will be pending.

1. Lack of compliance under 37 C.F.R. §§ 1.821-1.825.

Applicants submit a computer readable form of the Sequence Listing and amend the specification to enter SEQ ID NOs. in order to comply with the Notice Comply With Requirements For Patent Application Containing Nucleotide Sequences And/Or Amino Acid Sequences Disclosures dated February 26, 2004.

2. Objections to the specification.

Applicants amend the specification to obviate the Examiner's objection to the specification described in sections 8-10 of the office action. The hyperlink references are deleted. The trademarks are capitalized. The informalities pointed out by the Examiner in section 10 are corrected. In light of the amendments, the Examiner should withdraw the objections.

3. The rejections under 35 U.S.C. § 101 should be withdrawn.

The Examiner rejects Claims 32, 38-40, and 42-44 under 35 U.S.C. § 101, as allegedly not being supported by either a specific and substantial asserted utility or a well-established utility. Applicants respectfully disagree with the Examiner's contention and assert that the claimed method of Claims 32, 38-40, and 42-44 has a specific and substantial utility and that this assertion would be considered credible by one of ordinary

skill in the art.

Claims 32, 38-40, and 42-44 are directed to a method of diagnosing colorectal cancer in a human patient comprising: (a) obtaining a sample comprising colorectal tissue from a human patient; and (b) detecting the level of a polynucleotide encoding a CBF9 polypeptide in the sample, wherein the polynucleotide is an RNA equivalent of a nucleic acid sequence at least 90% identical to the nucleic acid sequence disclosed in SEQ ID NO: 1, and wherein an increase in the level of the polynucleotide relative to normal colorectal tissue is indicative of cancer.

The Examiner alleges that the specification does not teach "whether or not the "CBF9 gene" exhibits increased expression in colorectal cancer samples." (page 6, lines 8-9). The specification teaches that: "The results are shown in Table 1 and Table 2. The lists of genes come from colorectal tumors from a variety of stages of the disease. The genes that are up regulated in the tumors (overall) were also found to be expressed at a limited amount or not at all in the body map." (page 68, lines 13-16). Table 2 provides the CBF9 DNA sequence and CBF9 protein sequence (page 109-110). Further, the specification teaches that "[p]referably the colorectal cancer modulator protein is a product encoded by a gene of . . . Table 2" (page 3, lines 15-16).

The Examiner also alleges that "Applicant's application would merely provide the artisan with an invitation to perform further investigation, which might ultimately lead to a derivation of a specific benefit, or which might not; and in either case, an immediate benefit could not be derived from the use of the claimed invention because the existing information is insufficient to allow the artisan to use the disclosure in the manner asserted to provide an immediate benefit to the public." (page 7, lines 21-26). Applicants disagree with the Examiner's allegation, as the specification teaches that the levels of expression of the CBF9 nucleotide sequence or protein are preferred indicators of colorectal cancer.

The Examiner further alleges that: "Because the specification does not disclose a currently available, "real world" use for the claimed invention, the requirement set forth under 35 U.S.C. §101 have not been met." (page 10, lines 2-4). Applicants disagree with the Examiner's allegation, because determining the level of expression of CBF9 is an

indicator of the presence of colorectal cancer. Using the level of expression of CBF9 as an indicator of a disease state is a "real world" context of use.

Regarding having a specific and substantial utility, the claimed method of diagnosing colorectal cancer in a human patient comprising: (a) obtaining a sample comprising colorectal tissue from a human patient; and (b) detecting the level of a polynucleotide encoding a CBF9 polypeptide in the sample, wherein the polynucleotide is an RNA equivalent of a nucleic acid sequence at least 90% identical to the nucleic acid sequence disclosed in SEQ ID NO: 1, and wherein an increase in the level of the polynucleotide relative to normal colorectal tissue is indicative of cancer. Not all nucleotide sequences or proteins can function as markers of the presence of colorectal cancer. The levels of expressed SEQ ID NO:1 and its transcription and protein production can function as a marker of the presence of colorectal cancer. As the claimed method is to diagnose whether an individual has colorectal cancer, the claimed method has "real world" use and has specific and substantial utility.

Regarding having a credible assertion of utility, Applicants assert the utility of the Claims 32, 38-40, and 42-44 is credible. SEQ ID NO:1 encodes CBF9 protein. The expression of CBF9 is altered in colorectal cancer tissue (page 68, paragraph [274]). By comparing the level of expression of CBF9 in a sample tissue with the level of expression of CBF9 in a non-colorectal cancer tissue, one can determine whether the individual, from which the sample tissue was obtained, has colorectal cancer. This logic is not seriously flawed and the facts upon which the assertion is based are not inconsistent with this logic. One of ordinary skill in the art would accept that the claimed method of Claims 32, 38-40, and 42-44 is currently available for the use of diagnosing colorectal cancer.

For the foregoing reasons provided, Applicants submit that Claims 32, 38-40, and 42-44 have utility under § 101. The Examiner should withdraw these rejections.

In addition, for the foregoing reasons provided, Applicants submit that the rejections should not extend to the newly presented Claims 45-68.

4. The rejections under 35 U.S.C. § 112, first paragraph (enablement) should be

withdrawn.

The Examiner rejects Claims 32, 38-40, and 42-44 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. Applicants respectfully note that the Examiner appears to have erred in citing "section 10" (page 10, lines 13-14) and "sections 10 and 12" (page 10, lines 16). Applicants presume that the Examiner meant to cite "section 12" and "sections 12 and 14", respectively, and respond accordingly. Applicants traverse these rejections.

Applicants traverse the rejections in section 14 (page 10) in that, for the reasons provided in section 3 above, Claims 32, 38-40, and 42-44 have utility, and thus one of ordinary skill in the art, relying on the specification, would have sufficient disclosure to make and use the claimed methods.

Applicants also traverse the rejections of Claims 32, 38-40, and 42-44 in section 15 of the Examiner's office action (pages 10-11).

In regards to the rejections of Claims 32, 38-40, and 42-44, the Examiner relies on Skolnick, *et al.* (*TIB Tech* 18:34-9, 2000) to allege that "assigning functional activities for any particular protein or protein family based upon sequence homology alone is inaccurate" (page 11, lines 18-20). Skolnick, *et al.* disclose, as an example, the proteins of the serine-threonine-phosphatase superfamily "exhibit 40% or more sequence identity" between each other (page 35, Box 1). However, Skolnick, *et al.* do not specifically comment on the ability of one to predict the functional activities of proteins that have at least 90% identity. The claims are directed to a method of diagnosing colorectal cancer by determining the expression of a gene at least 90% identical to SEQ ID NO:1 in a first sample. Genes having at least 90% identity have a far greater degree of similarity than genes having only 40% of sequence similarity. Having at least 90% identity provides a far greater ability to predict the function activities of the encoded unknown protein. Applicants assert that testing a nucleotide sequence that is at least 90% identical to SEQ ID NO:1 is merely routine experimentation. The specification provides sufficient teaching regarding performing such routine experimentation. Thus, the specification provides sufficient teaching for one of ordinary skill in the art to make or use the claimed method.

Further, Applicants respectfully point out that the Examiner is mistaken in contending that "if [the specification is] enabling for practicing the methods of claims 32-44, wherein said method comprises determining the expression of a nucleic acid molecule comprising SEQ ID NO: 1, [then the specification] does not reasonably provide enablement for practicing the methods of claims 32-44 as presently claimed." (page 10, lines 15-21). The Examiner is mistaken as Claim 44 provides the limitation that the nucleotide sequence is SEQ ID NO:1. Therefore, according to the Examiner's own reasoning, this rejection should not apply to Claim 44.

For the foregoing reason provided, Applicants submit that Claims 32, 38-40, and 42-44 are fully enabled by the specification. The Examiner should withdraw these rejections.

In addition, for the foregoing reasons provided, Applicants submit that the rejections should not extend to the newly presented Claims 45-68.

5. The rejections under 35 U.S.C. § 112, first paragraph (written description) should be withdrawn.

The Examiner rejects Claims 32, 38-40, and 42-44 under 35 U.S.C. § 112, first paragraph as allegedly lacking sufficient written description. Applicants traverse these rejections.

The specification provides sufficient disclosure that reasonably conveys to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed methods. The Examiner relies on Skolnick, *et al.* in order to assert that art is unpredictable. As explained earlier, Skolnick, *et al.* do not specifically comment on the ability of one to predict functional activities of proteins that have at least 90% identity in their respective genes. Skolnick, *et al.* at most would lead one skilled in the art to believe that, when the sequence identity is 40% or less, the art is unpredictable. A 90% or more of sequence identity between two genes provides a far greater ability to predict function characteristics of the encoded unknown protein. Further, the specification also teaches the amino acid sequence (SEQ ID NO:2) encoded by SEQ ID NO:1 (pages 109-111,

Table 2). Table 2 also teaches the positions of start and stop codons (328-330 and 2749-2751, respectively) in SEQ ID NO:1 that correspond to the protein of SEQ ID NO:2 (page 109, lines 11-12). This provides further guidance to one skilled in the art in identifying nucleotide sequences with at least 90% identity with SEQ ID NO:1 that are suitable genes for diagnosing colorectal cancer using the claimed methods. Such a genus of genes would be reasonably conveyed by the disclosure of SEQ ID NO:1 in the specification.

For the foregoing reasons provided, Applicants submit that the specification provides sufficient disclosure that reasonably conveys to one skilled in the art that the inventors, at the time the application was filed, had possession of Claims 32, 38-40, and 42-44, and these rejections should be withdrawn.

In addition, for the foregoing reasons provided, Applicants submit that the rejections should not extend to the newly presented Claims 45-68.

CONCLUSION

In view of the foregoing amendment and remarks, the Applicants believe that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 463-8127.

Respectfully submitted,

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